REMARKS

Claims 1-14 and 35-51 are pending. Applicants have amended Claims 7, 11, and 36, support for which may be found in the specification as filed, *inter alia* at page 20, lines 21-22 No new matter has been added by this amendment. Applicants respectfully request reconsideration of the subject application in view of the preceding amendments and for the following reasons.

Rejection under 35 U.S.C. § 103(a)

Claims 1-14 and 35-51 have been rejected under 35 U.S.C. § 103(a) as being obvious over WO 92/13495 to Tripodi ("Tripodi"). Miyano et al., U.S. Patent No. 5,116,950 ("Miyano") is no longer cited as a secondary reference.

Applicants respectfully traverse this rejection and assert that the presently pending claims and remarks below obviate this rejection.

In order to establish a *prima facie* case of obviousness, three criteria must be met: First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach all the claim limitations. (See, MPEP 2143) The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Initially, applicants respectfully note that the claims define "the therapeutic composition effective on contact with thrombin at a site of treatment in a patient as a tissue adhesive, hemostat or sealant" by its components and characteristics of said components, as follows:

1. **non-autologous, non-single donor mammalian, clottable fibrinogen** recovered from a process [as recited in the claims] ... wherein said recovered fibrinogen polymerizes when provided in solution at said site at a therapeutically effective

fibrinogen concentration of about 10 mg/ml thereof or less, to a fibrin network having therapeutically effective strength,

wherein said therapeutically effective fibrinogen concentration at said site is about 10 mg/ml or less, and

2. **a sufficient amount of one or more physiologically-compatible solutes** such that said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25 mg/ml of said fibrinogen;

3. wherein **about 95%, or greater, of total protein present in said composition is fibrinogen**,

4. of which fibrinogen at least about **56% is clottable fibrinogen**.

Tripodi does not teach all of the above-recited claim limitations. The Examiner focuses on the process of making the fibrinogen component of the composition to reject the claimed composition, which is clearly defined by its components, as set forth above, in addition to reciting the process by which the fibrinogen component is recovered. The Examiner asserts that "the mere fact that the reference discloses a different means of obtaining a product is inconsequential since the reference discloses the same product, i.e. a fibrinogen composition. ... the reference discloses the same product, at the same concentration, that is useful for the same purpose." (February 17, 2004 Office Action, page 3, first full ¶)

The Examiner further asserts that "the reference discloses [sic] states that "fraction procedure describes produces a composition containing at least about 90 to about 98 percent fibrinogen with a low level of conversion to fibrin." (Examiner's emphasis) (Citing page 8, lines 25-34) [February 17, 2004 Office Action, page 3, second ¶) The Examiner concludes that:

> "the final composition overall would contain between 90-98% of fibrinogen. As for the clottable fibrinogen, the reference discloses a fibrinogen composition similar to applicants claims. **Therefore, the fibrinogen**

composition would necessarily have the [at] least 56% as clottable fibrinogen" [February 17, 2004 Office Action, Office Action, page 3, second ¶) [Applicant's emphasis]

Applicants respectfully maintain that the composition disclosed by Tripodi is not the same composition, as claimed, and as such Tripodi is not cited as an anticipatory reference. Nor is any teaching or suggestion provided by Tripodi to one of skill in the art to arrive at the claimed therapeutic composition comprising at least 56% clottable fibrinogen. Further, Tripodi provides no reasonable expectation of success of arriving at the claimed composition.

As noted in applicants' October 27, 2003 amendment, Tripodi describes that the fractionation procedure produces a "composition containing at least about 90 to about 98 percent fibrinogen with a low level of conversion to fibrin" (*See,* Tripodi, page 8, lines 25-28). The claimed composition, "wherein about 95%, or greater, of total protein present in said composition is fibrinogen" is distinguished from Tripodi's disclosed composition by the presence of **at least about 56% is clottable fibrinogen**. (Emphases added)

The Examiner's assertion that since Tripodi's final composition would contain between 90-98% of fibrinogen, therefore, the fibrinogen composition would necessarily have the at least 56% as clottable fibrinogen has no basis in Tripodi's disclosure, since Tripodi does not teach or suggest the determination of the percent of fibrinogen that is clottable in the composition described therein. In contrast, the subject specification provides clottablility determinations and the claimed invention is directed to a composition comprising fibrinogen of which fibrinogen at least about 56% is clottable fibrinogen. (See, Specification, page 18, line 20 - page 19, line 2 and Example 3 at page 46, line 8 - page 47, line19) In other aspects, the claimed therapeutic compositions, recite fibrinogen wherein "at least about 80% of the fibrinogen is clottable fibrinogen", [claims 42, 44, 46, 48 and 50], and wherein "about 90% or higher of the fibrinogen is clottable fibrinogen" [claims 43, 45, 47, 49 and 51].

As discussed in the subject specification, there are numerous reasons why at least a portion of the fibrinogen molecules derived from a purification process therefor may not be clottable, including denaturation. (See, Specification, page 18, lines 3-6) Further, the subject specification discusses that the presence of residual amounts and types of blood plasma proteins (copurified with the fibrinogen) that are present in the therapeutic compositions of

the present invention stablize fibrinogen, preserving its clottability and facilitating also resuspension thereof from lyophilized form. (See, Specification, page 18, lines10-16 and page 22, lines 2-18) Therefore, the process of recovering fibrinogen from a sample of blood plasma, as recited in the pending claims, produces fibrinogen comprising clottable fibrinogen of at least about 56% in addition to other proteins which copurify therewith. (See, Specification, page 20, lines 10-13 and 18–22).

Therefore, since a different process is used to obtain fibrinogen, as claimed[1], than that used by Tripodi, there is no certainty that even if Tripodi's composition comprises between 90-98% of fibrinogen, it would also necessarily **also** contain the same percentage of clottable fibrinogen, as presently claimed. (Emphasis added) Since Tripodi does not disclose the amount of clottable fibrinogen in his composition comprising fibrinogen, there is no basis to conclude that Tripodi's composition comprises fibrinogen, of which fibrinogen at least about 56% is clottable fibrinogen. Therefore, Tripodi does not teach all of the claimed limitations. Tripodi does not teach or suggest the claimed therapeutic composition, and further, Tripodi's disclosure would not lead to a reasonable expectation of success of arriving at the claimed composition.

Secondly, with respect to the another characteristic of the claimed fibrinogen component of the claimed therapeutic composition, Tripodi does not disclose "the recovered fibrinogen polymerizes when provided in solution at said site at a therapeutically effective

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[1]Independent Claims 1, 2, 13, 36 and 37, specify, in part, that the clottable fibrinogen is obtained from precipitating fibrinogen from a sample of non-human mammalian blood plasma with polyethylene glycol 1000 and reprecipitating the fibrinogen with glycine, wherein precipitation of the fibrinogen with polyethylene glycol is performed only **once**, such that at least about 90% of the fibrinogen present in the sample is recovered. (*See,* Specification at page 26).

In contrast, Tripodi describes precipitation of fibrinogen with PEG-800 that is conducted **twice**, and therefore, differs from the process to recover fibrinogen, as claimed.

The subject specification at page 27, states the precipitation of fibrinogen with PEG 1000, a low molecular weight PEG, leads to a cohesive fibrinogen precipitate that is more readily collected, for resuspension, than fibrinogen precipitate resulting from contact with, for example, PEG 8000, and further, that the use of low molecular weight PEG (such as PEG 1000) facilitates recovery of clottable fibrinogen.

fibrinogen concentration of about 10 mg/ml thereof or less, to a fibrin network having therapeutically effective strength, wherein said therapeutically effective fibrinogen concentration at said site is about 10 mg/ml or less" as claimed in claim 1. Tripodi, discloses neither a therapeutically effective fibrinogen concentration which polymerizes at a site of treatment to a fibrin network having therapeutically effective strength, nor a "therapeutically effective fibrinogen concentration at said site of about 10 mg/ml or less", as recited in claim 1, or "a therapeutically effective fibrinogen concentration at said site is about 30 mg/ml or less", as recited in claim 2. Therefore, there is no basis upon which to conclude that the composition described by Tripodi possesses such low concentrations at the treatment site which polymerize at said site to a fibrin network having therapeutically effective strength, as presently claimed. Therefore, Tripodi does not teach all of the claimed limitations. Moreover, nothing in Tripodi would teach or suggest to one of skill in the art the use of such low concentrations at a treatment site, nor would any disclosure in Tripodi lead one of skill to a reasonable expectation of success of arriving at a composition comprising this feature, as claimed.

Further, Tripodi does not mention anything about the rate of reconstitution from the lyophilized state of the composition described therein, whereas the claimed composition recites: "said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25 mg/ml of said fibrinogen". Therefore, Tripodi does not teach all of the claimed limitations. There is no teaching or suggestion by Tripodi of a rapid rate of reconstitution of the composition described therein, nor is there anything in Tripodi's disclosure which would lead one of skill in the art to arrive at this feature with an expectation of success.

Since Tripodi has not met the three criteria to establish a *prima facie* case of obviousness, Tripodi cannot render obvious the presently pending claims.

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

It is respectfully submitted that the subject application is in condition for allowance. A Notice of Allowance is respectfully requested.

The Examiner is invited to telephone the undersigned attorney at 212-425-7200 if it is believed that a discussion would advance the prosecution of this application.

Respectfully submitted,

Date: May 17, 2004

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